

**REMARKS**

Claims 1-28 are pending. Claim 1 has been amended to correct a clerical error and recite “combination” instead of “composition.” Claim 16 has been amended to recite that the molar ratio of l-amphetamine to d-amphetamine administered in a time period later in the day is higher than the ratio administered in a time period earlier in the day, and the time period later in the day is at least about one hour following the time period earlier in the day. Support for the amendment to claim 16 can be found in the specification at, for example, page 2, line 31 to page 3, line 1; page 3, lines 20-23; and page 5, line 13 to page 6, line 13.

**I. Objection to the specification**

The Examiner has objected to a hyperlink in the specification. The specification has been amended to delete this hyperlink. Thus, this objection should be withdrawn.

**II. The rejection under 35 U.S.C. § 112, second paragraph**

Claims 1-15 have been rejected under 35 U.S.C. § 112, second paragraph because claim 1 recites a pharmaceutical “composition” instead of a pharmaceutical “combination.” Claim 1 has been amended to recite “combination” instead of “composition.” Thus, this rejection should be withdrawn.

**III. The prior art rejections****A. Introduction**

According to the Examiner the release profile recited in the claims does not limit the claims. Thus, according to the Examiner, prior art that merely discloses l- and d- amphetamine anticipates or renders obvious the instant claims. *See*, Office Action, page 6.

The Examiner states that the “wherein” clause in the claims:

characterizes the function and/or effect of the composition after administration. In view of such, and further in view of the fact that the presence of the word ‘released’ is clearly indicative of a function of the composition that happens after administration, the instant ‘wherein’ clause has no limiting effect upon the claim.

*Id.*

According to the Examiner, a release profile is a non-limiting functional limitation because, the Examiner contends, release occurs after administration. Applicant respectfully disagrees. Release is often measured *in vitro* (see e.g., specification, page 4, lines 9-15). Thus, it can be measured prior to administration.

Further, a release profile is a physical property of the pharmaceutical combination. A physical property is a property even if it is not in its observable state. Using a non-scientific analogy, a person with blue eyes still has blue eyes even if the person is in a dark room and cannot be seen. Scientifically, a compound has properties like a melting point and a pH, whether or not the compound is exposed to its melting temperature (e.g., >300° for amphetamine) or in solution (for pH). See e.g., amphetamine in The Merck Index, 11<sup>th</sup> ed. 1989, p. 92, and p. ix, which identifies information such as melting point and pH as “physical data” (copy attached as Ex. 1). Similarly, a compound (or combination) can have a specified release profile as one of its properties. It does not matter whether the property is in its measurable state, i.e., in an appropriate *in vitro* or *in vivo* solution where the release occurs.

2. *Whether characterized as structural or functional, a release ratio can be measured and is limiting on the claimed combination*

According to the Examiner the “wherein” clause of claim 1 (i.e., “the molar ratio of l-amphetamine to d-amphetamine released from the pharmaceutical combination in a time period later in the day is higher than said ratio released therefrom in a time period earlier in the day”) “fails to set forth any physically or structurally limiting language other than the presence of a combination comprising l- and d- amphetamine.” Thus, the Examiner contends that the claim amounts to no more than a combination of l- and d- amphetamine.

Respectfully, the Examiner’s view of drug release is contrary to the ordinary understanding in the art, which recognizes drug release as a real and measurable property. For example, The United States Pharmacopeia, a gold-standard text, includes a chapter in its “Physical Tests” section entitled “Drug Release,” which provides methods to determine compliance with drug-release requirements provided in drug monographs. See The United States Pharmacopeia, The National Formulary, 2000, pages 1944-1951 (copy attached as Ex. 2). The instant claims recite

isomer release ratios, which can be measured in a variety of environments (see specification page 4, lines 9-15). Thus, those of ordinary skill in the art would understand that certain combinations may have release ratios falling within the claims and some may not. Moreover, the skilled artisan would know how to measure the ratio. Thus, the recited release profile is a measurable characteristic of the claimed combination that has a limiting effect.

B. The rejections under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1-11, 14-15 and 22-24 as anticipated by U.S. Patent No. 6,322,819. The '819 patent anticipates, according to the Examiner, because “[r]elease ratios of function, or in the present case, release, of the claimed composition, in the absence of a physical or structural difference, do not patentably limit the composition.” Thus, the instant claims “solely” require the presence of both l- and d- amphetamine, in base and/or salt form, in an effective amount.

The Examiner has maintained the rejections of claims 1-15 and 27-28 as anticipated by Patrick et al., “Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-Deficit Hyperactivity Disorder,” 1997, pp. 527-546. This rejection is based on the disclosure of ADDERALL®.

As explained above, the recited release ratio *is* limiting on the instant claims. The '819 patent and Patrick do not disclose or suggest a pharmaceutical combination wherein the ratio of l- to d- amphetamine is greater later in the day relative to a time period earlier in the day. Accordingly, the instant claims are not anticipated and this rejection should be withdrawn.

C. The rejections under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-28 as obvious over Patrick in view of WO2002/039998, the '819 patent, STN Registry No. 156-34-3, and Tulloch et al., Pharmacotherapy, 2002;22(11):1405-1415.

The Examiner contends that claims 16-20 do not recite increasing the release ratio of l- to d- amphetamine as the day progresses. Claim 16 has been amended to recite that the molar ratio of l- amphetamine to d-amphetamine administered in a time period later in the day is higher than the

ratio administered in a time period earlier in the day; and the time period later in the day is at least about one hour following the time period earlier in the day. No combination of the references discloses or suggests such a release pattern. Accordingly, this rejection should be withdrawn.

The Examiner acknowledges that claim 20 recites that the dose administered later in the day includes a greater amount of l-isomer than d-isomer, but contends that this limitation “is not commensurate in scope with what the Applicant alleges is the patentable distinction.” Office Action, page 9. The Examiner states that:

Applicant has failed to define when the later dose is administered, which, accordingly, means that a “later” dose is reasonably interpreted to be one that is given sequentially after the first dose, and not necessarily “later in the day” as Applicant asserts.

*Id.*

Applicant agrees that “later” is reasonably interpreted to be one that is given sequentially after the first dose. However, contrary to the Examiner, Applicant respectfully asserts that “later” does necessarily mean “later in the day” in the context of the claim. Claim 20 reads: “wherein two doses of amphetamine are administered to the patient in a day.” Thus, because the “later dose” is given after the “first dose,” and both doses are given “a day,” the “later dose” is necessarily administered later in the day (i.e., the dose given sequentially after the first dose cannot be given the next day).

The Examiner contends that the “Applicant has not raised any issues of material fact by addressing the discussion or motivation provided at pages 9-13 … of the previous Office Action” (Office Action, page 9). In the previous Office Action, the Examiner stated that Epstein discloses that l-amphetamine has fewer addictive properties and greater memory enhancing effects compared to d-amphetamine, and Tulloch discloses that the d/l ratio in ADDERALL® is 3:1 (Office Action mailed October 20, 2006, page 12). The Examiner stated that the references provided motivation to administer more l-isomer than d-isomer, or even all l-isomer, due to the enhanced efficacy and reduction in side effects (e.g., addiction) associated with the l-isomer (Office Action mailed October 20, 2006, page 12).

The instant claims recite a pharmaceutical combination wherein the molar ratio of l-amphetamine to d-amphetamine released from the combination in a time period later in the day is

higher than the ratio released from the combination in a time period earlier in the day. In the response to the October 20, 2006 Office Action, Applicant argued that: “[n]one of the prior art, whether alone or in combination, discloses or suggests increasing the release ratio of l- to d-amphetamine as the day progresses. Further, the prior art does not provide the motivation to one of ordinary skill in the art to vary the l- to d- release ratio as the day progresses in the claimed manner.” Response to Office Action dated March 1, 2007, pages 9-10 (emphasis in original). Thus, Applicant expressly raised and argued issues of material fact and motivation in the response to the previous Office Action, and repeats the arguments here for the Examiner’s consideration. No combination of the prior art references discloses or suggests a pharmaceutical combination wherein the ratio of l- to d- amphetamine increases as the day progresses.

According to the Examiner, Epstein discloses that l-amphetamine has fewer addictive properties and greater memory enhancing effects compared to d-amphetamine. Such a disclosure *teaches away* from the instant claims. This prior art provides an alternative, according to the Examiner, that is both more efficacious and safer, i.e., giving l-amphetamine only. Thus, there is no motivation to administer any d-amphetamine based on Epstein.

For the reasons stated above, this rejection should be withdrawn.

#### **IV. Provisional obviousness-type double patenting rejections**

The provisional rejection of claims 1-15 and 22-26 for obviousness-type double patenting over the composition claims of U.S. Patent Nos. 6,605,300; 6,322,819 or 6,913,768 and U.S. Patent Application Nos. 11/091,011; 10/758,151; 11/030,174 or 11/150,311 has been held in abeyance until allowable subject matter is identified.

#### **Conclusion**

No new matter has been added by these amendments. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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